Remarks

Status Of Claims

Claims 2-4 remain pending.

As previously presented, independent claim 2 is directed to a method of monitoring the effect of *in vivo* administration of a cathepsin S inhibitor to a subject, comprising: taking a blood sample of the subject; purifying the white blood cells from the sample; making whole cell lysates of the purified white blood cells; and analyzing the lysates for presence of a p10Ii fragment of invariant chain (Ii) by a suitable assay method, wherein the presence of the p10Ii fragment represents a block in degradation of the invariant chain due to inhibition of cathepsin S resulting from the *in vivo* administration of the cathepsin S inhibitor. Claim 3, which depends on claim 2, further recites that the assay method is Western blotting or enzyme-linked immunosorbent assay, and claim 4, which also depends on claim 2, further recites that the subject is a human.

Patentability Of Claims Under 35 U.S.C. § 103

In the outstanding Office Action, the rejection of claims 2-4 under 35 U.S.C. § 103(a), as being unpatentable over Chapman et al. (WO 99/58153) in view of Willmann et al. (US 6,495,333), was again maintained. As indicated by the Examiner in the earlier Office Actions, the Chapman et al. reference discloses a method for monitoring the effect *in vivo* of a cathepsin S inhibitor by detecting the presence of invariant chain Ii on the surface of a cell. According to the Examiner, Example III of the primary reference

discloses the evaluation of the effects of cathepsin S inhibitors on Ii degradation by obtaining a cell sample of splenocytes, lysing the cells, and then analyzing the lysates for the accumulation of an approximately 10 kDa fragment of Ii (i.e., pI0Ii). The Examiner noted that the claimed method differs from the Chapman et al. method in obtaining and purifying the white blood cells from a blood sample. The Examiner applied the secondary reference, Willmann et al., as supposedly suggesting the detection of fragment p10Ii as taught by Chapman et al. using peripheral blood samples as taught by Willmann et al., because the secondary reference recognizes the difficulty in studying function in dendritic cells on account of their rarity but shows ease in collecting blood as opposed to lymphatic tissue, and achieves the goal of non-invasive procedures in monitoring compound activity for pharmaceutical evaluation studies of autoimmune disorders such as in the method of Chapman et al. For the reasons provided below and in Applicant's previous replies, this rejection is in error.

Example III of Chapman et al. describes experimental methodology for analyzing the effects of cathepsin S activity on Ii chain degradation and MHC class II peptide loading using cathepsin S knockout mice to help establish the role of cathepsin S in Ii processing. Having shown that MHC class II complexes in splenocytes from -/- mice retain the p10Ii fragment, however, the methods described by Chapman et al. for monitoring the effects of cathepsin S inhibitors detect not the presence of the p10Ii fragment, but the presence or absence of the Ii chain, and not from a blood sample, but on a cell surface. See, e.g., Chapman et al., pages 13-14 and claims 35-51.

In an attempt to cure the deficiencies of the teachings of Chapman et al., the Examiner cited Willmann et al. as supposedly providing motivation for converting the cell-surface detection method of Chapman et al. to a blood-sample detection method. The Willmann et al. reference, however, discloses a flow cytometric method for measuring dendritic cell function in whole blood, not a method for monitoring the effect *in vivo* of a cathepsin S inhibitor administered to a subject, let alone of detecting a p10Ii fragment. Since the methods of the two references are for distinct types of assays, the artisan would not have been motivated to combine their teachings.

Lacking suggestion from the prior art to modify the Chapman et al. compound evaluation or diagnostic methods from detecting the presence or absence of the Ii chain on a cell surface to analyzing whole cell lysates of purified white blood cells from a blood sample for the presence of the p10Ii fragment as in the claimed invention, the Examiner again argued that "one cannot show nonobviousness by attacking references individually where the rejections are based on [a combination] of references". The burden is not on Applicant to "show nonobviousness" as suggested by the Examiner, however, but on the USPTO to show *prima facie* obviousness.

Moreover, the Examiner's argument mischaracterizes Applicant's previous replies. The Examiner should not discount Applicant's argument that the combined teachings of the references would have failed to motivate artisans to arrive at the claimed invention as an argument that the teachings of each reference by itself fails to suggest the invention. And the Examiner should not mistake the necessity of using hindsight to consider the merits of Applicant's claims in light of the prior art as permission for hindsight

reconstruction of Applicant's invention where, as here, the prior art fails to suggest the claimed invention as a whole.

Because the Examiner has not set forth a proper *prima facie* case of obviousness, the Section 103 rejection is in error and should be withdrawn.

Request For Acknowledgment Of IDS Submissions

Applicants again request the Examiner to initial the Forms PTO-1449 submitted with the Information Disclosure Statements dated November 26, 2001, and January 21, 2004, and return the initialed forms with the next official correspondence to confirm consideration of the cited references. Applicants further request the Examiner to do likewise with respect to the Supplemental Information Disclosure Statement dated September 2, 2005.

Conclusion

In view of the foregoing, claims 2-4 are allowable over the cited references. Accordingly, Applicants request prompt and favorable action.

Respectfully submitted,

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